ABSTRACT OF THE INVENTION

This invention provides unique members of the Hect family of ubiquitin ligases that specifically target BMP and TGFβ/activin pathway-specific Smads. The novel ligases have been named Smurf1and Smurf2. They directly interact with Smads1 and 5 and Smad7, respectively, and regulate the ubiquitination, turnover and activity of Smads and other proteins of these pathways. Smurf1 interferes with biological responses to BMP, but not activin signaling. In amphibian embryos Smurf1 inhibits endogenous BMP signals, resulting in altered pattern formation and cell fate specification in the mesoderm and ectoderm. The present invention provides a unique regulatory link between the ubiquitination pathway and the control of cell fate determination by the TGFβ superfamily during embryonic development. Thus, Smurf1 is a negative regulator of Smad1 signal transduction, by targeting Smad1, Smurf1 blocks BMP signaling. In mammalian cells, Smurf2 suppresses TGFβ signalling, and in Xenopus, blocks formation of dorsal mesoderm and causes anterior truncation of the embryos. Smurf2 forms a stable complex with Smad7, which induces degradation and downregulation of TGFβ/activin signalling.